Testosterone therapy for transgender men

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Testosterone therapy is a cornerstone of medical treatment for transgender men who choose to undergo it. The goal of testosterone therapy is usually to achieve serum testosterone concentrations in the male reference range. Testosterone has several desired effects as well as undesired and unknown effects. The desired effects include increased facial and body hair, increased lean mass and strength, decreased fat mass, deepening of the voice, increased sexual desire, cessation of menstruation, clitoral enlargement, and reductions in gender dysphoria, perceived stress, anxiety, and depression. Achievement of these goals comes with potential undesired effects and risks including acne, alopecia, reduced HDL cholesterol, increased triglycerides, and a possible increase in systolic blood pressure. An additional benefit of testosterone therapy (with or without mastectomy) is a reduced risk of breast cancer. Most of the effects of testosterone start to develop within several months of starting therapy, although facial hair and alopecia continue to develop after 1 year. A major limitation in the study of testosterone therapy for transgender men is a paucity of high-quality data due to a shortage of randomised controlled trials (partly because of ethical issues), few prospective and long-term studies, the use of suboptimum control groups, loss to follow-up, and difficulties in recruitment of representative samples of transgender populations.

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Introduction

Many transgender people seek medical care to obtain hormone therapy for masculinisation or feminisation. The mainstay of treatment is testosterone for a transgender man (also referred to as transman or female-to-male transgender) or oestrogen and antiandrogens for a transgender woman (also referred to as transwoman or male-to-female transgender). However, access to hormone therapy varies greatly by country and many transgender individuals do not choose to pursue hormone therapy. For example, findings from one study in Thailand showed that only 35% of transgender men were taking testosterone and that hormone therapy was often taken without medical supervision.[1] Testosterone therapy is typically started after puberty and might be initiated in mid-to-late adulthood for individuals coming to terms with their gender identity later in life.

Over the past few years, awareness and acceptance of transgenderism (also called transsexualism) has substantially increased in many countries, particularly those in western Europe, North America, and Australasia. Nevertheless, there are still many regions of the world where transgender individuals must keep their gender identity hidden due to lack of cultural acceptance, stigma, and overt discrimination. Barriers to receiving culturally competent transgender care are common. In 2015, a representative survey of endocrinologists (n=80) in the mid-Atlantic region of the USA found that 59% did not have any transgender patients under their care, only 50% felt somewhat or very comfortable discussing gender identity or sexual orientation, and 33% did not feel competent to provide transgender care.[2]

Estimation of the true prevalence of transgenderism is difficult because some transgender individuals come to terms with their gender identity later in life and others do not openly identify as transgender because of societal pressures and stigmatisation. A 1996 study of patients treated at a specialised gender clinic in the Netherlands estimated a prevalence of one in 12 000 men assigned male at birth and one in 30 000 women assigned female at birth.[3] In 2010, results from a population-based household probability study of more than 28 000 adults in Massachusetts, USA, showed that one in 215 people identified as transgender.[4]

Transgenderism has a biological component, as evidenced from anatomical and genetic studies. Data from one anatomical study showed that the volume of the central subdivision of the bed nucleus of the stria terminalis in transgender women was similar to that of natal (also referred to as non-transgender) women rather than non-transgender men.[5] Results of a genetics study that included 23 pairs of identical twins and 21 pairs of non-identical twins showed 39% concordance of transgenderism between identical twins and 0% between non-identical twins.[6] Nonetheless, the precise genetic foundations of transgenderism are not clear. Investigators have examined several sex hormone-related genes, including CAG repeat length in the androgen receptor gene, CA repeat length in the oestrogen receptor β gene, and TTTA repeat length in the aromatase gene. Although results from some of these studies have suggested an association between transgenderism and particular genetic variations, findings have not been replicated in other studies and the evidence is inconclusive.[7–9]

In this Review, I focus on the effects of testosterone therapy on various organ systems in adult transgender men. Because the extent of the effects of testosterone can vary by type of testosterone formulation, this information is included where possible. Where applicable, comparisons will be made with the effects of testosterone therapy in men with hypogonadism and natal women. These comparisons have limitations because of the different host environment in natal men and the lower doses of testosterone that are given to natal women. Importantly, endogenous testosterone concentrations are generally 10–20 times higher in men than in women. Detailed information about the diagnostic criteria for transgenderism or gender dysphoria and general care has been

published by the World Professional Association for Transgender Health[10] and in clinical guidelines from the Endocrine Society[11] and the Royal College of Psychiatrists.[12] Table 1 shows a summary of the recommendations and evidence quality from the Endocrine Society's clinical practice guidelines. A major limitation in the study of transgender medicine is a paucity of high-quality data. Difficulties in obtaining such data stem from the scarcity of randomised controlled trials (partly because of ethical issues), few prospective and long-term studies, the use of suboptimum control groups, loss to follow-up, and difficulties in recruitment of representative samples, including people disenfranchised from society and medical care. In this Review I do not address care of transgender adolescents, which may include suppression of the gonadal axis for a period of time before hormone therapy is started.

Intended effects of testosterone therapy

Overview

The overall goals of testosterone therapy for transgender men are to obtain secondary sexual characteristics of natal men, to live their lives as men, to improve their wellbeing, and to decrease gender dysphoria. Because androgen receptors are widely distributed, testosterone therapy has diverse effects throughout the body, affecting both physical and psychological characteristics (figure). No standard practice exists for starting doses or maintenance doses of testosterone. In clinical practice, I usually initiate therapy at a low dose (ie, 50 mg intramuscular testosterone cypionate every 2 weeks) and gradually increases the dose to a full adult male replacement dose (ie, 200 mg intramuscular testosterone cypionate every 2 weeks), as if treating a man with hypogonadism. Periodic hormone measurements are obtained to aid in the titration. Testosterone therapy is generally regarded as safe in the short term, but much less is known about its long-term effects. Table 2 shows the doses, advantages, and disadvantages of the principal formulations of testosterone that are available around the world. Although many formulations of testosterone exist, research about transgender men has mainly been restricted to intramuscular esters, long-acting intramuscular testosterone undecanoate, and topical gels. The effects of testosterone therapy in transgender men should not be generalised to men with hypogonadism or postmenopausal women, who are given much lower doses.

Body composition and strength

Testosterone therapy changes body composition towards that of natal men who, on average, have more muscle and less fat than do natal women. Specifically, the magnitude of increase recorded during 1–2 years of testosterone treatment across several studies was 2·2–3·5 kg in bodyweight, 1·7–6·0 kg in lean mass, and 0·8–2·0 kg/m² in BMI.[13–19] Results from most studies[13,14,18,19] showed a decrease in fat mass of 2·3–4·0 kg. However, investigators of some studies[15,16,18] noted no change in BMI with the intramuscular testosterone undecanoate formulation. In one prospective study,[18] intramuscular testosterone undecanoate therapy given for more than 1 year increased grip strength by 18%, as well as increasing the cross-sectional area of the forearm and calf muscles.

	Quality of evidence
Before hormone therapy	
Confirm the diagnostic criteria of gender dysphoria or transgenderism and the eligibility and readiness criteria	Moderate
Evaluate and address medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment	Moderate
During hormone therapy	
Maintain cross-sex hormone concentrations in the normal physiological range for the desired gender	Low
Review the onset and time course of physical changes induced by cross-sex hormone treatment	Low
Implement regular clinical and laboratory monitoring every 3 months during the first year and then once or twice per year	Low
Measure complete blood count and liver function tests at baseline and every 3 months for the first year and then one to two times per year thereafter; monitor weight, blood pressure, lipids, fasting blood sugar (if family history of diabetes), and HbA_{1c} (if individual has diabetes) at regular visits	Not stated
Assess bone mineral density if risk factors for osteoporosis exist, specifically in those who stop hormone therapy after gonadectomy	Moderate
Do an annual Pap smear if cervical tissue is present	Not stated
Consider mammograms if mastectomy is not done	Not stated
Assess transgender people treated with hormones for cardiovascular risk factors	Low
Before surgery	
Assess the risks and benefits of inclusion of total hysterectomy and oophorectomy as part of sex reassignment surgery	Very low
Consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the mental health professional find surgery advisable	Very low
Genital sex reassignment surgery to be recommended only after completion of at least 1 year of consistent and compliant hormone treatment	Very low
The physician responsible for endocrine treatment should medically clear transgender individuals for sex reassignment surgery and collaborate with the surgeon on hormone use during and after surgery	Very low

Table 1: **Recommendations from the Endocrine Society's clinical practice guidelines[11]**

Distinguishing the effects of testosterone from those of oestrogen on body composition can be complex because testosterone is converted to oestradiol via aromatisation. To clarify the effects of the different sex steroids, a 16 week study[20] was done in healthy young natal men (mean age 33 years) who all received a gonadotropin-releasing hormone agonist to suppress endogenous sex steroids. They were given various doses of testosterone replacement with or without an aromatase inhibitor. Changes in lean mass, thigh-muscle area, and leg-press strength were mostly related to total testosterone concentrations, whereas increased subcutaneous and intra-abdominal fat were related to oestrogen deficiency.

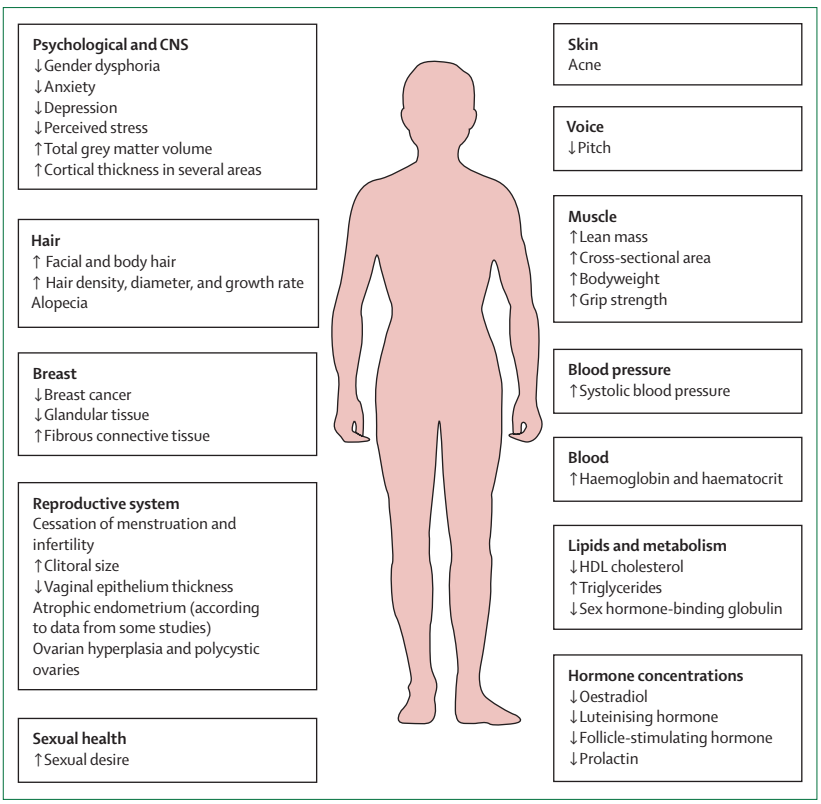

Figure: **Effects of testosterone therapy in transgender men**

Skin and hair

One of the most important intended effects of testosterone therapy is the development of facial and body hair. However, this hair growth is often accompanied by acne. Androgens interact with pilosebaceous units in the skin to produce these effects and, in transgender men who are genetically predisposed, can cause alopecia. Whereas facial hair and acne develop within months of starting testosterone, androgenetic alopecia is a long-term effect of androgen use. In a study[21] that included 17 transgender men given intramuscular testosterone esters, investigators noted progressive increases in the median Ferriman-Gallwey hirsutism score from 2 at baseline to 11 at 4 months, to 13 at 8 months, and to 16 at 12 months. Testosterone progressively increased hair density, growth rate, and diameter at the cheek and upper abdomen. Although the hair changes began within 4 months of initiation of therapy, hair diameter did not reach that of natal males by 12 months. Based on the Leeds classification system, the prevalence of physiological acne at baseline was 31% at the face and 19% at the back, increasing to 94% at the face and 88% at the back after 4 months of androgen therapy.

Facial hair, androgenetic alopecia, and acne were also assessed with validated instruments in a prospective study of 20 transgender men who took intramuscular testosterone undecanoate for 1 year and in a cross-sectional study of another 50 transgender men who had been on various testosterone formulations for about 10 years.[22] In the prospective study, the median Ferriman-Gallwey score increased from 0·5 at baseline to 12·0 at 1 year, with inter-individual variability from 2 to 25. In the cross-sectional study of long-term treatment, the median Ferriman-Gallwey score was 24, with a range of 6 to 34. One of 20 individuals developed mild frontotemporal hair loss during the prospective study, based on the Norwood-Hamilton classification system for hair loss. By contrast, long-term testosterone therapy resulted in mild frontotemporal hair loss in 33% (16/50) of participants and moderate-to-severe alopecia in 31% (15/50). Based on the Gradual Acne Grading Scale, prevalence of facial acne increased from 35% at baseline to 82% at 1 year, with a corresponding increase in back or chest acne from 15% to 88%. Despite the high prevalence of acne at 12 months, acne scores peaked at 6 months, with much lower scores seen at 12 months and after long-term testosterone use.

In another prospective study of 53 transgender men who took intramuscular testosterone undecanoate for 1 year,[19] 17% of participants developed androgenetic alopecia, based on the Norwood-Hamilton classification system. In this study, no cases of severe acne were reported and topical or oral acne medications were initiated by 18 (34%) participants. In another study of transgender men who used intramuscular testosterone undecanoate for 24 months,[15] 16% (7/45) of individuals developed so-called troublesome acne.

Although alopecia is an undesirable effect for some transgender men, it can be desirable for others because it is considered a masculine feature. For those at risk or bothered by alopecia, treatment with a 5α-reductase inhibitor can be used, but potential users should be made aware of evidence showing persistent sexual and other side-effects in otherwise healthy young men and that potential adverse effects on masculinisation in transgender men have not been well studied.[23,24]

Reproductive system

Testosterone therapy is associated with changes to serum concentrations of reproductive and pituitary

	Route	Dosing	Advantages	Disadvantages
Enanthate or cypionate	Intramuscular	100–200 mg every 2 weeks (or half dose weekly)	Inexpensive Effective at achieving target testosterone concentrations	Peaks and troughs with pharmacokinetics Pain with injections Increased erythrocytosis compared with other formulations
Gels (1%)	Topical	25–100 mg per day	Consistent testosterone concentrations	Expensive Potential transference to women or children on personal contact
Patch	Topical	2·5–10 mg per day	Consistent testosterone concentrations	Expensive Skin irritation Inadequate testosterone concentrations
Axillary solution	Topical	30–120 mg per day	Consistent testosterone concentrations	Expensive
Undecanoate	Intramuscular	750–1000 mg every ten to 14 weeks	Consistent testosterone concentrations Infrequent dosing	Expensive Large injection volume Risk of pulmonary oil microembolus (rare)
Undecanoate	Oral	40–80 mg, 2–3 times per day with meals	..	Variable testosterone concentrations
Pellets	Subcutaneous implants	150–450 mg every 3–6 months	Consistent testosterone concentrations Infrequent dosing	Expensive Invasive (incision with scalpel) Bleeding Infection Inflexible dosing
Buccal	Buccal	30 mg twice per day	..	Expensive Gum irritation Taste alterations Fall off
Nasal spray	Nasal	11 mg three times per day	..	Expensive Frequenct dosing Inadequate testosterone concentrations

Availability of certain formulations varies by country.

Table 2: **Testosterone formulations**

hormones. In addition to an expected rise in testosterone, oestrogen concentrations often decrease to 70–301 pmol/L (19–82 pg/mL), with an accompanying decrease in sex hormone-binding globulin.[15,16,18,19,21,22,25,26] The magnitude of the reduction in sex hormone-binding globulin is similar between the various modes of testosterone delivery. Most large studies have shown testosterone therapy to be associated with reduced, but not totally suppressed, gonadotropins (luteinising hormone and follicle-stimulating hormone) and reduced prolactin concentrations.[15,16,19]

As with facial hair, one of the most sought-after effects of testosterone therapy is the cessation of menstruation, which can be an unpleasant reminder of the presence of female body parts. In a study[27] of 138 transgender men who took three different doses of intramuscular testosterone enanthate ranging from 125 mg every 2 weeks to 250 mg every 2 weeks, cessation of menstruation was noted by 86–97% of participants by 6 months. In a study of 45 transgender men randomly assigned either intramuscular testosterone esters, testosterone gel, or intramuscular testosterone undecanoate,[16] time to amenorrhoea ranged from 30 to 41 weeks, with all participants reporting amenorrhoea by 1 year.

Another desired early physical sign of testosterone therapy is clitoral enlargement, which can be accompanied by pain. In a 1 year prospective study of transgender men given intramuscular testosterone undecanoate,[19] clitoral pain was noted by 20% (5/25) of participants and peaked at 6 months of therapy. In another study,[28] a mean maximal clitoral length of 4·6 cm was recorded after 1 year of testosterone cypionate treatment.

Testosterone therapy typically induces changes to the vagina, endometrium, and ovaries. In one study, transgender men taking intramuscular testosterone esters had thinner vaginal epithelia in which a loss of the intermediate and superficial layers had occurred, compared with premenopausal and postmenopausal women.[29] Other findings include loss of intracytoplasmic glycogen, reduced expression of oestrogen receptor α and oestrogen receptor β, and reduced cellular proliferation as measured by Ki-67 immunostaining. Two studies[30,31] examining the effects of testosterone on the endometrium had inconsistent results. One of the studies,[30] of 104 patients given testosterone enanthate for 2–9 years, showed two distinct patterns: half of the participants had proliferative endometrium and half had atrophic endometrium. One case of endometrial adenocarcinoma was identified. In the other study,[31] which included 27 transgender men who received intramuscular testosterone esters for 1–6 years, all participants had inactive endometrium similar to that of postmenopausal

women. With respect to the ovaries, testosterone therapy results in stromal hyperplasia and mean volumes of 10–11 mL, which is significantly larger than that of natal women not on testosterone. 80% of patients had histological characteristics of polycystic ovary syndrome, if a definition of more than 12 antral follicles per ovary was used.[30]

Some transgender men wish to have children and therefore to remain fertile. In one study[32] of 50 transgender men who had all undergone sexual reassignment surgery (also called gender-affirming surgery), 27 (54%) wanted to have children, although not necessarily biological children. In some countries, many transgender men choose to undergo hysterectomy and bilateral oophorectomy, whereas in other countries many do not undergo any sexual reassignment surgery. Fertility options also depend on the sexual orientation of the individual, since a male partner can potentially provide sperm and a female partner can potentially become pregnant with donor sperm. Transgender men who have not had sexual reassignment surgery might be able to become pregnant after discontinuing testosterone therapy. A web-based study[31] of 25 transgender men, mostly from the USA, assessed participants who experienced pregnancy and delivered a neonate after female-to-male gender transition. 24 (96%) participants resumed having menstruation within 4 months of stopping testosterone treatment. 5 (20%) actually had no menses before pregnancy. A major limitation of this study was that one of the inclusion criteria was a successful birth, so the results cannot be generalised to all transgender men who discontinue testosterone, because some will not be fertile. For transgender men who undergo sexual reassignment surgery, fertility options should be discussed before any surgery is done. In theory, patients who choose surgery can have cryopreservation of oocytes or ovarian tissue for future use, but there has been little published about this approach. Notably, pregnancy improved gender dysphoria for some transgender men, but worsened it for others.[32,33]

Breasts

Testosterone therapy alters the composition of breast tissue in transgender men. Using tissue obtained from mastectomies as part of the surgical management of transgender men, investigators of two studies of intramuscular testosterone esters[30,34] showed a substantial reduction of glandular tissue and an increase in fibrous connective tissue. A reduced amount of adipose tissue was noted compared with menopausal women.[34]

In addition to mastectomies that are routinely done in many countries, testosterone therapy in transgender men also reduces the incidence of breast cancer. No cases of atypical hyperplasia or carcinoma were seen in two studies of transgender men given long-term testosterone therapy, of which one included 100 participants treated for 2–9 years[30] and the other included 23 participants treated for 18–24 months.[34] No cases of breast cancer were seen in a Dutch retrospective study[35] of 365 transgender men who received testosterone therapy for a mean of 19 years. The same Dutch research group later reported one case of breast cancer among 795 transgender men (mean age 23 years at start of hormone therapy) who received testosterone for a mean of 20 years.[36] The estimated incidence rate for breast cancer was 5·9 cases per 100 000 person-years in transgender men taking testosterone, compared with 154·7 cases per 100 000 person-years in natal women.

Likewise, incidence of breast cancer was significantly lower in premenopausal and postmenopausal women given subcutaneous testosterone pellet implants for various symptoms (mean age 52 years).[37] The serum concentrations of testosterone achieved[37] were supra-physiological for women and close to the lower end of the reference range for natal men.

Sexual health

Testosterone therapy is associated with increased sexual desire in both transgender men and postmenopausal women with low libido who receive lower doses of testosterone.[25,38,39] This effect is probably biological because it is seen in blinded randomised controlled trials.[40] Results of a prospective study of 50 transgender men without psychiatric disorders who were given various types of testosterone for 1 year showed increased frequencies of desire, sexual fantasies, arousal, and masturbation.[25] However, no changes were seen in frequency of sexual activity with a partner or with relationship satisfaction. In a retrospective study of 138 transgender men who received testosterone therapy for a mean of 7 years,[41] 71% reported an increase in sexual desire, whereas 12% had a decrease and 17% had no change. Although most of these participants underwent hysterectomy, oophorectomy, and phallo-plasty, no difference was reported in sexual desire between those with or without phalloplasties. In another retrospective study of 45 transgender men who had undergone sexual reassignment surgery at least 1 year before the study,[38] 32 (74%) had increased scores for sexual desire and 11 (25%) had no change while on testosterone therapy.

Data from most observational studies and testosterone trials have shown a link between testosterone concentrations and female sexual function.[42] In a randomised controlled trial of 814 postmenopausal women with low libido, those who received a testosterone patch (300 µg per day) without oestrogen therapy had a small increase in the number of satisfying sexual episodes per month, increased desire, and decreased distress.[39] Nonetheless, a few studies (including unpublished ones) of transdermal testosterone gels have not shown a benefit for sexual function or desire.[40]

Voice

Similar to changes that occur in boys going through puberty, the increased levels of testosterone in transgender men on testosterone therapy are associated with a lowering of the pitch of the voice. A longitudinal retrospective study[43] collected voice data on 50 transgender men, of whom 36 had data from baseline to 12 months on testosterone therapy. The largest drop in mean fundamental frequency occurred during the first 2–5 months of testosterone therapy. Nonetheless, 24% of transgender men received vocal therapy due to symptoms of vocal fatigue, vocal instability, strained voice quality, insufficiency lowering of pitch, voice projection difficulties, and problems with the voice sounding younger than the subjects' chronological age.[43] In one cross-sectional study,[44] voice parameters were compared between 40 transgender men who had been on long-term testosterone therapy (mean >10 years) and a control group of natal men. Acoustically, 90% of transgender men had voices indistinguishable from those of natal men. Nonetheless, 10% of transgender men had either a gender ambiguous fundamental frequency between 150 and 185 Hz when reading or had undergone voice therapy or surgery.

Psychological and cognitive effects

Androgen and oestrogen receptors are distributed throughout the central nervous system, and testosterone therapy is generally associated with improved overall wellbeing in transgender men. Although some of the improvements to mental health could be related to the effects of testosterone, a more likely explanation is the reduction in gender dysphoria associated with hormone therapy, since both transgender men and transgender women experience beneficial effects irrespective of the differences in hormone therapy.[45] In a prospective study, the psychological functioning of transgender men before starting hormone therapy was worse than that of non-transgender male and female control groups. After 3 months of testosterone therapy, transgender men showed improvements on several scales (depression, hypochondria, hysteria, and paranoia) of the validated Minnesota Multiphasic Personality Inventory compared with the control groups.[46]

In another prospective study,[45] investigators assessed depression, anxiety, and psychological symptoms of 29 transgender men using three validated instruments (Zung Self-Rating Depression Scale, Zung Self-Rating Anxiety Scale, and Symptom Checklist 90-Revised) before and after 1 year of treatment with intramuscular testosterone esters. In both trangender men and trangender women, treatment was associated with a reduction prevalence of anxiety (from 53 [50%] individuals to 18 [17%]), depression (from 45 [42%] individuals to 24 [23%]), and various symptoms on several scales on the Symptom Checklist 90-Revised. The same research group reported that 1 year of therapy with intramuscular testosterone esters was associated with reduced levels of perceived stress and a decrease in mean morning serum cortisol concentrations from 772 nmol/L to 413 nmol/L (28 µg/dL to 15 µg/dL).[47] In another study,[48] investigators measured the prevalence of anxiety, depression, and social distress using validated instruments (Hospital Anxiety and Depression Scale and Social Anxiety and Distress Scale), comparing 38 transgender men (and 29 transgender women) who had not begun hormone therapy and 36 transgender men (and 84 transgender women) who had been taking various formulations of testosterone for an average of 5 years. Compared with individuals (the study combined the results for both transgender men and transgender women) who had not begun hormone therapy, those receiving hormone therapy had lower prevalence of anxiety symptoms (33% [39/120] *vs* 61% [41/67]), depression symptoms (8% [10/120] *vs* 31% [21/67]), and social distress. By contrast with the previous studies, investigators of a prospective study[25] of 50 transgender men without psychiatric disorders who were given various types of testosterone for 1 year noted no changes to mood, depression, happiness, temper, or anger, based on a non-validated questionnaire.

The effects of testosterone therapy on cognition in transgender men have been poorly studied. Some data for premenopausal and postmenopausal women suggest that low doses of testosterone therapy result in improvements in various cognitive functions. For example, in a double-blind, placebo-controlled trial[49] of a single dose of sublingual testosterone in young women, (age range 20–32 years) visuospatial ability was improved 4–5 h after they had ingested the testosterone. Similarly, in a 26 week randomised controlled trial[50] of transdermal testosterone gel in postmenopausal women (age range 55–65 years) not on oestrogen, the results showed improvements in verbal learning and memory. The testosterone concentrations achieved in the trial[50] were at the upper limit of normal for premenopausal women.

Concordant with changes in cognition and behaviour seen with testosterone therapy, imaging has revealed physical changes in the size of various brain structures and areas during testosterone therapy. In one such study,[51] researchers used MRI to compare the brain structure of 15 transgender men before and after at least 6 months of cross-sex hormone therapy. Testosterone treatment was associated with increased total grey matter volume and bilateral increased cortical thickness in the postcentral gyrus, in the cuneus and rostral middle frontal areas on the right lobe, and in the inferior parietal, lingual, pericalcarine, and supramarginal regions on the left lobe.

Bone

Both oestrogen and testosterone have important roles in bone health. Although testosterone therapy often results in a decrease in mean oestradiol concentrations in transgender men compared with natal women, testosterone is also converted into oestradiol by

aromatase in several tissues, including bone.[15,16,18,19,21,22,25,26] Oestrogen is needed to maintain adequate bone health and to prevent the rapid bone loss that would otherwise occur after menopause.

Compared with age-matched natal women, 50 transgender men receiving testosterone therapy for an average of 10 years were reported to have increased radial cortical bone size and decreased cortical volumetric bone mineral density at the radius and tibia.[52] In a 1 year prospective study of 23 transgender men given intramuscular testosterone undecanoate,[18] areal and volumetric bone parameters remained largely unchanged, apart from small increases in trabecular volumetric bone mineral density at the distal radius and bone mineral density at the total hip. A potential explanation is that increased muscle mass induces an increased mechanical load on the bone, which might stimulate bone formation. In another study,[53] transgender men taking testosterone had reduced bone mineral density after oophorectomy, with the decrease inversely associated with serum concentrations of luteinising hormone and follicle-stimulating hormone.

In addition to the positive effects on bone mineral density seen with oestrogen use by postmenopausal women, evidence suggests that androgens provide further bone support. In a randomised controlled trial of various combinations of oral conjugated equine oestrogen with or without methyltestosterone,[54] the oestrogen and androgen combination increased bone mineral density at the spine and hip more than did oestrogen alone.

However, it is important to note that bone mineral density is a surrogate marker for fracture, which is the endpoint of real clinical interest. Trials showing a benefit of testosterone therapy with respect to fracture rates are lacking not only in transgender men, but also in hypogonadal men and postmenopausal women.

Potential risks of tesosterone therapy

Cardiometabolic risk factors

To provide some context, the cardiovascular benefits and risks of testosterone therapy for natal men with low or low-normal testosterone concentrations are poorly understood and controversial. The cardiovascular effects of testosterone might be mediated via several mechanisms, including changes to insulin sensitivity, lipid profiles, inflammatory cytokines, salt retention, polycythaemia, and platelet aggregation.[55] In a 3 year randomised controlled trial that included 308 older men (mean age 68 years) with low or low-normal testosterone concentrations,[56] topical testosterone therapy did not affect the rate of change in common carotid artery intima-media thickness or coronary artery calcium deposition. In a large retrospective study of more than 83 000 male US veterans (mean age 64 years) with low testosterone concentrations[57] reduced incidences of myocardial infarction, stroke, and all-cause mortality were seen in men who achieved normal testosterone levels on therapy compared with untreated men and men who were treated but did not have normalisation of testosterone levels. Conversely, data from two studies have shown an increase in cardiovascular events associated with testosterone therapy. In a randomised controlled trial of 209 community-dwelling older men (mean age 74 years) with mobility limitations and total testosterone concentrations of 100–350 ng/dL (3·5–12·1 nmol/L), free testosterone concentrations of less than 50 pg/mL (173 pmol/L), or both,[58] men given topical testosterone had more than five times as many cardiovascular-related events, which were broadly defined to include events such as raised blood pressure, oedema, and electrocardiogram changes. In the second study,[55] investigators examined the association between testosterone prescriptions and incidence of acute myocardial infarction in a large health-care database. Irrespective of baseline testosterone concentrations, which were not known, men aged 65 years and older who received testosterone prescriptions had a doubling of acute myocardial infarction in the 90 days after receiving the prescription, compared with the period before receiving the prescription. In view of the controversy surrounding cardiovascular risk associated with testosterone treatment in natal men, there is concern that this potential risk might also apply to transgender men given testosterone formulations.

The lipid parameter most consistently affected by testosterone therapy in transgender men is HDL cholesterol, which is reported to decrease by 0·10–0·34 mmol/L (4–13 mg/dL) during 1 year of testosterone therapy, irrespective of formulation.[14–17,19] Findings from some studies[15,17,19] have also shown an increase in triglycerides of 0·07–0·36 mmol/L (6–32 mg/dL) during 1 or 2 years with topical testosterone and intramuscular testosterone undecanoate. The evidence is inconsistent with respect to total cholesterol and LDL cholesterol. In one study of intramuscular testosterone esters,[14] substantial increases in both total cholesterol (0·62 mmol/L [24 mg/dL] at 1 year and 1·04 mmol/L [40 mg/dL] at 2 years) and LDL cholesterol (0·28 mmol/L [11 mg/dL] at 1 year and 0·93 mmol/L [36 mg/dL] at 2 years) were reported after 1 and 2 years. Hypogonadal men given testosterone therapy might also develop reduced HDL cholesterol concentrations, but triglycerides are not usually affected.[59]

None of the testosterone formulations seem to have an effect on fasting serum glucose or insulin sensitivity, as measured by homoeostatic model assessment–insulin resistance.[13,14,16,19,60] By contrast, decreased insulin sensitivity has been reported in hypogonadal men not receiving testosterone therapy and in women with polycystic ovarian syndrome who have increased endogenous androgen levels.[61,62] The evidence is inconsistent with respect to fasting serum insulin concentrations, with separate studies showing increases, decreases, or no change.[14,16,19]

Investigators of one case-control study[63] noted that testosterone therapy in transgender men was associated with increased incidence of type 2 diabetes, although no effect on obesity was seen. Results of a study of 12 patients who took intramuscular testosterone esters for 6 months showed reduced serum concentrations of leptin and adiponectin at the end of the study.[13]

Findings from some studies[14,15,19] have shown that, in transgender men, testosterone therapy for 1 year is associated with an increase in systolic blood pressure of 4–12 mm Hg, but no significant change in diastolic blood pressure. In one study of 97 patients using either topical testosterone or intramuscular testosterone undecanoate[17] no changes were seen in either systolic or diastolic blood pressure during a 2 year period. Although rates of cardiovascular events do not seem to be increased in the short term, the implication of increased systolic blood pressure is unknown in the long term. The main challenge in establishing whether raised systolic blood pressure is associated with an increased incidence of cardiovascular events is the age of transgender men studied as most begin testosterone therapy before the age of 30 years, when the risk of such events is exceedingly low. Long-term data about transgender men who started testosterone in early adulthood are scarce, as are short-term data about transgender men who started testosterone when they were older than 50 years. Notably, increased blood pressure is not a major concern for hypogonadal men on testosterone replacement. The results of a systematic review and meta-analysis[59] showed that testosterone therapy in hypogonadal men was not associated with changes in blood pressure. Likewise, the Endocrine Society guidelines on treatment of androgen deficiency[64] do not mention increased blood pressure as a potential adverse effect in this population.

In a retrospective study of 50 transgender men who received testosterone for an average of 10 years,[65] no cardiovascular events such as myocardial infarction or stroke occurred. In the same study, in which an increased prevalence of type 2 diabetes among transgender men was reported,[63] the investigators also compared the prevalence of cardiovascular disease between 138 transgender men, who had been on testosterone for an average of 9 years, and age-matched natal women, showing no differences in myocardial infarction or cerebrovascular disease. It is important to note that 86% of transgender men had hysterectomy or oophorectomy in addition to mastectomy. In a systematic review and meta-analysis of hormone therapy in transgender populations,[66] very few reported cardiovascular events (deaths, strokes, myocardial infarctions, or venous thromboembolism) were identified, but the quality of the evidence was very low and the data were inconclusive. Ultimately, because of the potential for testosterone to increase cardiovascular events in transgender men, research needs to be done in older transgender men rather than in younger individuals who are at low risk of cardiovascular events.

All formulations of testosterone therapy increase the haemoglobin concentration and hematocrit but rarely to levels consistent with erythrocytosis. Greater increases are seen with intramuscular esters than with other formulations, consistent with studies in hypogonadal men given testosterone replacement.[67] Topical testosterone for 1 year resulted in a mean rise in haemoglobin of 6 g/L (0·6 g/dL) and a mean rise in haematocrit of 2%.[16] Intramuscular testosterone esters resulted in a mean rise in haemoglobin of 17 g/L (1·7 g/dL) and a mean rise in haematocrit of 4·7% in 1 year.[16] Intramuscular testosterone undecanoate for 1 year resulted in a mean rise in haemoglobin of 12–13 g/L (1·2–1·3 g/dL) and a mean rise in haematocrit of 3·3–5·0%.[15,16,19,23] No further increases were seen after 1 year.[15]

Testosterone therapy does not seem to be associated with increased incidence of venous thromboembolism in transgender men, but studies have not been sufficiently powered to address this issue. Results from one study[68] showed testosterone to be antithrombotic with lower activated protein C resistance in transgender men given testosterone. In a group of 89 transgender men with a mean age of 27 years and 62 (70%) of whom smoked, who were given intramuscular testosterone undecanoate and lynestrenol, with a mean follow-up of 47 months, no cases of venous thromboembolism occurred.[69] Results from a study of premenopausal women with premenstrual symptoms who were given low doses of testosterone via subcutaneous implants for at least 2 years[70] showed no effects on clotting factors. Nonetheless, in 2014, on the basis of post-marketing reports, the US Food and Drug Administration required manufacturers of testosterone products for men to include a general warning about the risk of venous blood clots unrelated to polycythaemia.[71] A retrospective study[65] of 50 transgender men who received testosterone for an average of 10 years showed no deep vein thrombosis events.

Mortality

No prospective studies have been done to investigate mortality rates in transgender men, and the studies that have been reported have had inconsistent results. In one study done in the Netherlands,[35] researchers compared standardised mortality rates between 365 transgender men who were all on testosterone therapy and the general population and noted no differences. The transgender group started testosterone therapy at a mean age of 26 years and had a mean follow-up of 19 years on hormone therapy. In a Swedish population-based registry study,[72] investigators used data from a national death registry between 1973 and 2003 to compare mortality rates between 133 transgender men (who had received both hormone therapy and gender reassignment surgery) and 1330 random population controls matched by age and birth sex. Mortality rates seemed to be similar during the first 10 years after gender reassignment surgery, but the curves diverged

Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Scopus for articles published in English and Spanish from Jan 1, 2000, to April 5, 2016. The search terms used were "transgender", "transsexual", or "gender dysphoria" in combination with the terms "testosterone" or "androgen". Abstracts of articles resulting from these searches and relevant references cited in those articles were reviewed. Case reports and small case series of less than ten individuals were only included if the findings were deemed very important. Selected older publications were also included based on importance.

after 10 years, with transgender men having increased mortality rates. The adjusted hazard ratio for suicide was 19·1 (95% CI 5·8–62·9) for transgender men and transgender women combined as mortality data were not broken down by gender.

Conclusions

Within several months of starting testosterone therapy, transgender men begin to notice many desired effects, including increased facial and body hair, increased lean mass and strength, decreased fat mass, deepened voice, increased sexual desire, cessation of menstruation, clitoral enlargement, and reductions in gender dysphoria, perceived stress, anxiety, and depression. The most common undesired effect is acne, for which many patients take topical or oral medications. The main physical feature that testosterone therapy does not address is the presence of breast tissue, although some atrophy might occur. Many transgender men elect to undergo so-called top surgery to remove their breasts or wear a binder to flatten their chests. Many of the effects of testosterone therapy have also been noted in natal hypogonadal men and postmenopausal women with low libido who are given testosterone. Nonetheless, the effects in transgender men should not be generalised to other populations because of the different anatomical and hormonal background of natal men and the lower testosterone doses used for natal women. For example, the dose of testosterone used for postmenopausal symptoms is not associated with clitoromegaly, increased muscle mass, or deepening of the voice.[73]

Testosterone therapy seems to be quite safe in the short term, based on results from many studies. Nonetheless, testosterone decreases HDL cholesterol, increases triglycerides, might increase systolic blood pressure, and might increase the incidence of diabetes and metabolic syndrome. The long-term consequences of these changes are not known. In view of the substantial reduction in the risk of breast cancer associated with testosterone therapy, there is no clear evidence to guide the interval of screening mammography. The few studies that compare mortality rates of transgender men with those of the general population have yielded inconsistent results. Since transgender medicine is a fairly new field, more research is needed, especially in the form of larger and longer prospective studies that include diverse populations.

Declaration of interests
I declare no competing interests.

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